

Isoniazid-Related Fatal Hepatitis

TO THE EDITOR: The recent article by Millard and colleagues on fatal isoniazid hepatitis (June 1996 issue) was a thorough survey of all cases of death reportedly due to isoniazid chemoprophylaxis.¹ They used data from the Public Health Service to assess the death rate attributed to isoniazid, which they estimated to be 4.2 per 100,000 people started on therapy since 1972 and 1.7 per 100,000 treated since the current monitoring guidelines were established.² This is the most accurate estimate we have to date for the magnitude of risk for fatal isoniazid hepatitis, which is substantially lower than was previously thought.³ The death rate that they found for monitored prophylaxis is similar to that seen in a previous study and is equivalent to the rate for death due to hepatitis of any cause in the general population.^{4,5}

A major error made in this study was the use of the number of people completing therapy as the denominator for all the deaths found to calculate their risk of death, which was estimated to be as high as 7 per 100,000. A review of each of the deaths indicated that essentially all had occurred during the course of treatment or within days of discontinuing the drug before completing therapy. It is clear that those people who successfully finish a full course of treatment and survive have no further risk for drug-related death. Any figures used in this article describing their risk for death should be ignored.

SHELLEY R. SALPETER, MD
Division of Primary Care
Department of Medicine
Santa Clara Valley Health Center
750 S Bascom Ave
San Jose, CA 95128

REFERENCES

1. Millard PS, Wilcosky TC, Reade-Christoper SJ, Weber DJ: Isoniazid-related fatal hepatitis. *West J Med* 1996; 164:486-491
2. American Thoracic Society: Treatment of tuberculosis and other mycobacterial diseases. *Am Rev Respir Dis* 1983; 127:790-796
3. Kopanoff DE, Snider DE Jr, Caras GJ: Isoniazid-related hepatitis: A US Public Health Service Cooperative Surveillance Study. *Am Rev Respir Dis* 1978; 117:991-1001
4. Salpeter SR: Fatal isoniazid-induced hepatitis—Its risks during chemoprophylaxis. *West J Med* 1993; 159:560-564
5. National Center for Health Statistics: Vital Statistics of the US, 1988—Vol II, Mortality, Pt A. Washington, DC, US Public Health Service, 1991, pp 10-162

* * *

Drs Millard and Wilcosky Respond

TO THE EDITOR: Fatal hepatitis from isoniazid administered as a single agent for the prevention of tuberculosis is a rare event. The debate about just how rare has continued since the first reports of death from isoniazid-associated hepatitis in the early 1970s.¹ Although our study provides the best evidence to date concerning the case rate of fatal isoniazid-associated hepatitis among public sector patients, it has a number of limitations with regard to both the numerator (incomplete ascertainment of cases and possible misclassification of cause of death) and denominator. Ideally, the death rate would be expressed in terms of the number of deaths per person-time of isoniazid administration (for example, deaths per 100,000 person-months); unfortunately, only estimates of the total number of patients starting and completing therapy are available.² Dr Salpeter correctly points out that people who have completed therapy are no longer at risk of isoniazid-associated hepatitis. Likewise, people who have stopped taking isoniazid before completing their course of therapy are no longer at risk. For this reason, we calculated two rates: the death rate per 100,000 persons beginning therapy (an underestimate) and the death rate per 100,000 persons completing therapy (an overestimate). Recognizing the uncertainties in our data, we think that the "right" rate lies between 4.2 per 100,000 persons beginning therapy and 7.0 per 100,000 persons completing therapy.

PETER S. MILLARD, MD, PhD
Family Practice Residency Program
Eastern Maine Medical Center
417 State St, Ste 100
Bangor, ME 04401-6600

TIMOTHY C. WILCOSKY, PhD
Epidemiologic and Medical Studies Program
Research Triangle Institute
Research Triangle Park, NC 27709

REFERENCES

1. Maddrey WC, Boitnott JK: Isoniazid hepatitis. *Ann Intern Med* 1973; 79:1-12
2. Snider DE Jr, Caras GJ: Isoniazid-associated hepatitis deaths: A review of available information. *Am Rev Respir Dis* 1992; 145(Pt 1):494-497